

REMARKS

Claims 1-4, 7, and 8 are pending in the present application.

Claims 5 and 6 were previously canceled without prejudice or disclaimer.

Claim 1 has been amended to remove terms of intended use. No new matter has been added.

Rejections Under 35 U.S.C. § 103(a)**II**

Claim 7 stands rejected under 35 U.S.C. §103(a) in view of *Keller et al.* ("*Keller*") and *Doi et al.* ("*Doi*") (WO 98/31343), *Bjermer et al.* ("*Bjermer*"), and *van der Molen et al.* ("*Molen*"). It is alleged that the requirements for a *prima facie* case of obviousness have been satisfied because: (a) *Keller* "discloses medicinal or pharmaceutical aerosol compositions comprising beta-mimetics and corticoids;" (b) *Bjermer* and *Van der Molen* "teach that β 2 agonists ... are used as inhalations in asthma treatment, and should be given in combination with corticosteroids;" and (c) *Doi* "discloses that loteprednol etabonate is known in the method of treating inflammatory conditions or allergy (asthma bronchiale ...)" (see Official Action, at page 8, lines 4-20). Based on (a) - (c), it is alleged that persons skilled in the art would have been motivated to combine loteprednol and beta-mimetics.

Applicants traverse the rejection of Claim 7 under 35 U.S.C. § 103(a), and submit that a *prima facie* case of obviousness has NOT been established by the Examiner as required under the MPEP §2143. The MPEP §2143 provides that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1)

there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure." (MPEP sec. 2143 quoting *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Claim 7 is directed to a method for the treatment of asthma bronchiale in a patient, the method comprising:

administering to the patient an efficacious amount of

(i) loteprednol or loteprednol etabonate and

(ii) at least one β_2 adrenoceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts thereof,

wherein a pharmaceutically acceptable excipient or a vehicle is added if suitable for simultaneous, sequential or separate administration.

Applicants assert that none of the cited references suggest the combination of the elements of the method recited in Claim 7. *Keller* does not disclose a method for treating asthma bronchiale by co-administering the combination of (i) loteprednol or (loteprednol etabonate) and (ii) β_2 adrenoceptor agonists as pharmaceutically effective agents, as recited in Claim 7. In a previous Official Action, the Examiner acknowledged that "Keller does not expressly disclose the employment of the inhalable medicinal aerosol composition comprising the combination as instantly

claimed ...," and which is acknowledged again in the present Official Action (see lines 1-4, at page 4 of the Office Action of 1/24/2006).

Furthermore, *Bjermer*, *Doi*, and *Molen*, do not individually disclose/suggest the co-administration of the combination of (i) luteprednol (or luteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale, as recited in Claim 7. If none of the cited references discloses or suggests the co-administration of the combination of (i) luteprednol (or luteprednol etabonate) and (ii) β_2 adrenoreceptor agonists as pharmaceutically effective agents for treating asthma bronchiale, as recited in Claim 7, then who is combining these elements?

Under the MPEP §2143, a *prima facie* case of obviousness is established when three basic criteria have been satisfied: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The Examiner bases the rejection of Claim 7, on a mere allegation of "reasonable expectation of treating asthma" without establishing point (1) that requires a showing of some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Furthermore, the Examiner cites *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980, for holding that combining "two compositions, each of which is taught by the

prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art" is deemed to be prima facie obvious. Applicants point out that the relevant facts have been stretched in favor of the Examiner's conclusion of the obviousness of the method of Claim 7. Of all cited references, only *Doi* describes a composition comprising loteprednol in particular, and *Doi*'s composition is formulated for use as a nasal suspension, and the possibility of using the composition for the treatment of any type of asthma, let alone asthma bronchiale, in not mentioned. The Examiner states that "*Doi* discloses that loteprednol etabonate is known to be useful in a pharmaceutical composition and a method of treating inflammatory conditions or allergy since loteprednol etabonate has excellent anti inflammatory conditions or antiallergic activities and is value as a drug in an ointment or a liquid form, and loteprednol etabonate is formuated into a long-term stable liquid suspension for nasal administration" (Official Action, page 5, last paragraph). Based on this, the Examiner alleges that "one of ordinary skill in the art could have been motivated to employ loteprednol etabonate in combination with reproterol, salmeterol, or formoterol in a method for the treatment of allergies and/or airway disorders such as asthma bronchiale" (emphasis added). If *Doi* is the only cited reference that discloses the use of loteprednol etabonate, and if *Doi* does not describe the use of the loteprednol etabonate-containing nasal drips for the treatment of "airway disorders such as asthma bronchiale," then how is the holding of *In re Kerkhoven* relevant here, when the purpose of *Doi* (anti-allergic agent) is not the same purpose as the method of Claim 7 (treatment of asthma bronchiale)? Applicants submit that absent a teaching from the cited references to combine (1)

loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor, a *prima facie* case for obviousness has not been established. Thus, Applicants respectfully request the withdrawal of the rejection of Claim 7.

II

Claims 1-4 and 8 stand rejected under 35 U.S.C. §103(a) in view of *Keller et al.* ("*Keller*") (WO 9834595, English Equivalent to U.S. Patent No. 6,461,591) and *Palmer Douglas* ("*Palmer Douglas*") (EP 0416950). It is alleged that *Palmer Douglas's* process for making dry powder formulation comprising classical corticosteroids and beta-mimetics can be utilized for producing the claimed powdered pharmaceutical composition comprising loteprednol or loteprednol etabonate, and at least one β_2 adrenoreceptor agonist.

Applicants traverse the rejection of Claims 1-4 and 8 under 35 U.S.C. § 103(a), and submit that a *prima facie* case of obviousness has NOT been established by the Examiner as required under the MPEP §2143.

Claim 1 reciting: A powdered pharmaceutical composition (as amended), comprising:

formulated separately or together,
an efficacious amount of (i) loteprednol or loteprednol etabonate; and (ii) at least one β_2 adrenoreceptor agonist selected from the group consisting of salbutamol, reproterol, salmeterol, formoterol, and pharmaceutically tolerable salts thereof,
for simultaneous, sequential, or separate administration by inhalation, wherein the pharmaceutical composition is formulated in a powdered form.

Applicants assert that *Keller* and *Palmer Douglas* do not suggest the combination of the elements of independent Claim 1. *Keller* does not disclose the

claimed pharmaceutical composition comprising a combination of (i) loteprednol or loteprednol etabonate and (ii) β_2 adrenoreceptor agonists. *Keller* merely provides a list of pharmaceutically active compounds that may be included in their aerosol formulations (see Col. 7 of *Keller*). *Keller* discloses only pressure-liquefied propellant mixtures for the preparation of aerosols formulated for administration by using pressurized inhalants (see Table 1, Col. 12 of *Keller* and Examples 1-14, Cols. 11-14 of *Keller*). Again, Applicants point out that *Keller* does not disclose the claimed powdered formulations comprising: (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists. Applicants note that pressure-liquefied aerosol formulations are different from powdered formulations recited in Claims 1-4.

Palmer Douglas does not remedy the deficiencies of *Keller*. Under the MPEP §2143, a *prima facie* case of obviousness is established when three basic criteria have been satisfied: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all claim limitations. Because *Palmer Douglas* does not disclose loteprednol or loteprednol etabonate, *Palmer Douglas* cannot be relied on to demonstrate point (3) - the teaching of all claim limitations, or point (1) - the suggestion/motivation to modify or combine the reference teachings. Because a *prima facie* case for obviousness has not been established, Applicants respectfully request the withdrawal of the rejection of Claims 1-4.

Applicants traverse the rejection of Claim 8 under 35 U.S.C. § 103(a), and assert that *Keller* and *Palmer Douglas* do not suggest the combination of the elements of independent Claim 8, *inter alia*, (i) loteprednol or loteprednol etabonate and (ii) at least one β_2 adrenoreceptor agonists. For the same reasons explained above for the traversal of Claims 1-4, because a *prima facie* case for obviousness has not been established, Applicants respectfully request the withdrawal of the rejection of Claims 1-4.

Technical Distinctions, Synergistic Results, and Comparative Tests

Applicants are submitting two technical documents with this Amendment in order to point out that the compounds referred to as "loteprednol" and "corticoids" (classic steroids) can be structurally and functionally different. Loteprednol etabonate is structurally distinguishable from other corticosteroids in that the ketone group at number 20 position is not present in loteprednol etabonate that confers high lipid-solubility for enhancing penetration into cells (See attached "Physicians' Desk Reference: OPT - Alrex Ophthalmic Suspension 0.2% (Bausch & Lomb), at page 2 of 7). The low toxicity of loteprednol etabonate is attributed to the formation of inactive metabolites within the bodies of patients. In addition, Applicants have attached an excerpt from Drugdex Evaluations in order to show that Loteprednol ("soft steroids") is distinguishable from the classical steroids having a different mechanism of action that leads to greater toxicity effects (see page 11 of 17).

Applicants note that at the time of the present invention, loteprednol was appreciated mainly for ophthalmic clinical applications, and the possibility of utilizing loteprednol etabonate in combination with beta-mimetics for the treatment of asthma bronchiale had not been appreciated. Furthermore, the synergistic effect of the combination of loteprednol etabonate and beta-mimetics (as shown in Tables 1 and 2) was unexpected.

Furthermore, Applicants have distinguished the properties of soft corticosteroids (from that of classical corticosteroids) in the Specification by explaining that soft corticosteroids, such as loteprednols or loteprednol etabonates, are more readily metabolized (inactivated) *in vivo* by engaging a different metabolic pathway compared to classical corticosteroids, such as beclomethasone dipropionate (BDP) or budesonide (BUD), which are known to have relatively higher *in vivo* stability resulting in many deleterious side effects experienced by patients (see lines 21-31, at page 2 of the Specification). Applicants have further explained differences in the side effects produced by classical corticosteroids and soft corticosteroids to distinguish the claimed compositions and methods from the prior art (see lines 10-30, page 7 of the Specification). The claimed combination is especially beneficial for children who are especially sensitive to the deleterious side effects caused by classical corticosteroids, which includes growth retardation, osteoporosis, and an increase in intraocular pressure.

Furthermore, Applicants submit that the Office has not fully appreciated the experiments performed by the Applicants, as shown in the Specification. These experiments provide unexpected advantages, resulting from the co-administration of (1) loteprednol (or loteprednol etabonate) and (2) β_2 adrenoceptor agonists. The

specification provides data showing synergistic effect caused by the co-exposure to a mixture of (1) loteprednol or loteprednol etabonate; and (2) β_2 adrenoceptor agonists, under *in vitro* and *in vivo* conditions. The specification provides comparative data showing a less deleterious effect by loteprednol in comparison to classical corticosteroids. The specification also provides comparative data showing enhanced therapeutic effect by loteprednol in comparison to classical corticosteroids.

Table 1 of the specification shows *in vitro* synergistic (over-additive) effect (44%) of the mixture of loteprednol and salbutamol on blood cells as measured by the level of inhibition on TNF-alpha release, compared to samples exposed only to either loteprednol (1%) or salbutamol (17%) alone (see page 5 of the Specification).

Table 2 shows *in vivo* synergistic effect (36 - 65%) of a mixture of loteprednol and formoterol on guinea pigs as measured by the level of inhibition of eosinophilia, compared to samples exposed only to either loteprednol (11-22%) or formoterol (4-20%) alone (see page 6 of the Specification).

Table 3 shows gross reduction in thymus mass in rats exposed to classical corticosteroids, including fluticasone (65%), beclomethasone (51%), and budesonide (89%), in comparison to loteprednol (15-28%). This suggests that the co-administration of loteprednol in combination with β_2 adrenoceptor agonists would likely produce the over-additive effect exemplified in Tables 1 and 2 in patients, while providing advantages for avoiding some of the deleterious side effects associated with classical corticosteroids that have been well-documented in the prior art, including the cited references (see page 8 of the Specification).

Table 4 shows enhanced therapeutic breadth after long-term exposure to loteprednol (45.5) in comparison to modest or low therapeutic efficacy observed for

classical steroids, such as fluticasone (33) and budesonide (5) (see page 10 of the Specification).

Examples 1-8 are also provided. In light of the above discussion, Applicants respectfully request the withdrawal of the rejection of Claims 1-4, 7 and 8 under 35 U.S.C. §103(a).



CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of present application may be expedited.

Respectfully submitted,

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